*Shiga*-toxin by the *S. dysenteriae* 1, is wholly or partly removed or permanently inactivated; and

(C) a *Shigella* comprising an inactivated *Shiga*-toxin gene.]

## REMARKS

Reconsideration of the application is respectfully requested.

Claims 1-8, 10, 13-21, 23, and 24 are pending. Claim 17 has been amended to clarify the invention. The Amendment adds no new matter.

Claims 1-8, 10, 13-21, 23, and 24 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to adequately teach one skilled in the art how to make and/or use the claimed invention. The Examiner argues that the construction of claimed *Shigella* mutants requires knowledge of the nucleotide sequence of said genes, which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted. The Examiner alleges that due to the limited teaching of the specification and the unpredictable nature of which mutations are useful, one skilled in the art can not practice the invention as claimed absent undue experimentation, citing Ex parte Gardner, In re Cavallito, and In re Lund.

The Examiner further asserts that, while it would appear that techniques are known in the art for inactivation of genes, it is not routine to screen for positions within the DNA sequence of the gene so that it does not invade the cells, does not spread within infected cells, or does not

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produce toxins. The Examiner contends that the specification does not disclose which regions of the genes are responsible for biological activity, the number of nucleotides which must be deleted or inserted, the identity of the genes responsible for invading cells, and the identity of genes that code for use of aerobactin and enterochelin; that more than one gene would be expected to be involved in toxin production, spreading, and/or invasion; and that the specification gives no guidance as to which of the essentially infinite choices would be successful. The Examiner concludes that modifications that can be made to inactivate genes is unpredictable, and that undue experimentation would be required to practice the claimed invention, citing Ex parte Forman.

The Office also cites In re Deuel as indicating that the general process of isolating DNA does not mean that the claimed specific compound was precisely envisioned or obvious. In addition, the Office contends that applicants' arguments are not sufficient to overcome the rejection in view of Fiers v. Sugano and Amgen v. Chugai Pharmaceutical Co., Ltd. The Office further contends that the references provided by applicants are not sufficient to overcome the rejection, alleging that the exhibits are not commensurate in scope with the claimed invention.

Applicants respectfully traverse the rejection. Applicants submit that the mutagenesis technique taught by the specification does not require knowledge of the nucleotide sequence of the target genes, does not require knowledge of regions of genes responsible for biological activity, and that the number of nucleotides deleted or inserted is not critical to the practice of the

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claimed invention for the reasons stated in applicants' April 17, 1998, Amendment and Response.

Prentki and Krisch, 1984, which was submitted with the April 17, 1998, Amendment and Response, discloses a method of *in vitro* insertional mutagenesis used by the applicants in embodiments of the claimed invention. (Specification at 9-23.) As submitted in the April 17, 1998, Amendment and Response, the technique disclosed in Prentki and Krisch allows mutagenesis by insertion of a selectable marker (**interposon**) at any restriction site in a plasmid, the insertion of the interposon abolishes mRNA synthesis and interrupts protein synthesis, no sequence information of the target gene is required, no knowledge of the regions of genes responsible for biological activity is required, and the number of nucleotides deleted or inserted is not critical to the practice of the claimed invention.

The Office responded to applicants' submission by quoting from Prentki and Krisch regarding difficulties with **transposon mutagenesis**. Applicants respectfully submit that the method of Prentki and Krisch is **not transposon mutagenesis**, but an alternative to transposon mutagenesis involving an **interposon**. As Prentki and Krisch states on page 312, ¶2:

> The construction of a DNA fragment that facilitates in vitro insertional mutagenesis has been described in this communication. This fragment enables one to mutagenize under conditions where use of transposons is not appropriate . . .

Furthermore, as recited in claim 1, the claimed method is "other than only by inactivation by means of a transposon inserted into the genes". Therefore, applicants submit that the quotation

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used by the Office to allegedly demonstrate that the method disclosed by Prentki and Krisch does not enable the claimed invention is not relevant to enablement of the claimed method by the method disclosed by Prentki and Krisch since the claimed invention is **not** a method of transposon mutagenesis.

As applicants previously submitted, the insertion of an interposon by the method of Prentki and Krisch introduces both transcriptional and translational stop signals, which **abolishes** mRNA synthesis and interrupts protein synthesis. Prentki and Krisch at 307. All insertions of the interposon into the LacZ gene of plasmid placB235 **totally abolished** B-galactosidase activity. Id. at 309 and Table 1. Furthermore, Prentki and Krisch indicate that the most important aspect of the mutagenesis procedure is the selectable introduction of translational and transcriptional stop signals. Id. at 312. The selectable marker can be subsequently removed by restriction enzyme digestion and ligation, indicating that the size of the insertion is not critical to the practice of this technique. Id., Figure 5. As previously submitted, **no sequence information of the target gene was required** to obtain the desired mutants in Prentki and Krisch, and **no knowledge of the regions of genes responsible for biological activity was required** in Prentki and Krisch. In addition, **the size of the insertion is not critical to the practice of this technique**. Therefore, applicants submit that the skilled artisan expects success in practicing the claimed invention, and that the claimed invention is predictable and requires no undue experimentation.

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Applicants further submit that the skilled artisan would expect that deletion of a large segment of a gene will result in complete loss of protein production. See Brock and Madigan, 1991 (Exhibit 1), page 239, column 1, paragraph 3. Similarly, applicants submit that the skilled artisan would expect that any insertion or deletion of a base in a gene will result in a frameshift mutant, which would completely upset the translation of the gene. See Brock and Madigan, page 239, column 2, paragraph 1. Applicants submit that, due to the fact that codons are defined by triplets of nucleotides, the generation of useful frameshift mutants is predictable and does not require undue experimentation. Accordingly, applicants respectfully request withdrawal of the rejection.

Applicants further submit that the previously submitted references indicate the level of skill in the art prior to the filing of the instant application with regard to genes involved in the invasion, spread and toxicity of *Shigella*. Applicants note that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Applicants note that the claims are directed towards a **method of modifying** the genes of *Shigella*. Applicants have disclosed embodiments that enable the use of the claimed **method**. The skilled artisan recognizes that the claimed **method** can be used to modify a wild strain of *Shigella* using any gene necessary for the invasion, spread, or toxicity of *Shigella*, absent evidence to the

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contrary. Therefore, applicants submit that the claimed **method** is broadly applicable, and that no undue experimentation is required in its use.

Applicants note that they are not required to disclose every species encompassed by their claims, even in an unpredictable art. In re Angstadt, 537 F.2d 498, 502, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Rather, applicants can meet the sufficiency of disclosure through illustrative examples by teaching the skilled artisan to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. In re Vaeck, 947 F.2d 488, 496, 20 U.S.P.Q. 2d 1438, 1445 (Fed. Cir. 1991). As in In re Angstadt, applicants have not disclosed every species that will work with the claimed invention. As the court stated in In re Angstadt:

> To require such a complete disclosure, would apparently necessitate a patent application or applications with "thousands" of examples . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

In re Angstadt, 537 F.2d at 502, 190 U.S.P.Q. at 218. Therefore, applicants submit the disclosure of all genes capable of working in the claimed invention is not required. Applicants submit that the teachings and embodiments of the specification provide the requisite knowledge for the skilled artisan to practice the claimed invention.

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Applicants further submit that the skilled artisan is capable of determining, without undue experimentation, which genes can be used in the claimed **method**. For example, the skilled artisan could merely choose from those genes identified in the specification or the prior art as being necessary for the invasion, spread, or toxicity of *Shigella*, and inactivate these genes using the teachings of the specification. As detailed above, the skilled artisan expects success in generating useful deletion and insertion mutants, and no undue experimentation would be required by the skilled artisan. Furthermore, the skilled artisan could determine which mutants were unable to invade, spread, or kill cells using the methods cited in the specification and known in the prior art, as previously described in the April 17, 1998, Amendment and Response.

Applicants also submit that Exhibits 10, 11, and 15, which were submitted with the April 17, 1998, Amendment and Response and are directed to *E. Coli* aerobactin genes, are relevant to the level of skill in the art with regard to *Shigella* aerobactin genes since, as indicated in the abstract of Lawlor and Payne, 1984 (Exhibit 12 of the April 17, 1998, Amendment and Response), the *Shigella* aerobactin genes share considerable homology with the *E. Coli* aerobactin genes. Similarly, applicants submit that the skilled artisan would recognize that Exhibits 13 and 14, which were submitted with the April 17, 1998, Amendment and Response, are relevant to the corresponding *Shigella* genes.

Applicants further submit that, unlike the invention at issue in Ex parte Forman, applicants have claimed a method, which can be used to predictably generate the desired mutants.

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Applicants respectfully submit that the Office's reliance on In re Deuel, Ex parte Forman, Ex parte Gardner, In re Cavallito, In re Lund, Fiers v. Sugano, and Amgen v. Chugai Pharmaceutical Co., Ltd. in support of the rejection under 35 U.S.C. § 112, first paragraph, is improper. Applicants respectfully submit that the cited cases are not relevant to enablement of the claimed **method and strains produced by that method**, since the cited cases concern the enablement of claims to specific compounds, claimed *per se* without reference to a process. Applicants note that compounds, processes, and products-by-process are treated differently in the analysis of enablement, as well as obviousness. See Fiers v. Sugano, 984 F.2d 1164, 1171, 25 U.S.P.Q. 2d, 1601, 1605 (Fed. Cir. 1993); See also In re Deuel, 51 F.3d 1552, 1558, 34 U.S.P.Q. 2d 1210, 1215 (Fed Cir. 1995). Claim 17 has been amended to more clearly indicate that the claimed strains are products produced by the process of claim 1.

Applicants submit that the prior art discloses a wealth of information concerning the genes involved in the spread, invasion, and toxicity of *Shigella*, as well as routine methods for assaying such genes. Using the disclosure of these references in combination with the teachings of the specification, the skilled artisan could practice the claimed invention without undue experimentation. Accordingly, the claimed invention is fully enabled, and applicants respectfully request withdrawal of the rejection.

Claims 13 and 14 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter, which was not described in such a way as to reasonably convey to one

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skilled in the art that the inventors, at the time the application was filed, had possession of the claimed subject matter. The Office contends that there is no support for claiming a *Shigella* mutant wherein the *Shigella* is other than SC501, SC504, SC505, and SC506.

Applicants traverse the rejection. In order to determine the appropriate disclosure of an application, "the specification as a whole must be considered." In re Wright, 866 F.2d 422, 424, 9 U.S.P.Q. 2d 1649, 1651 (Fed. Cir. 1989). Furthermore, there is no particular way in which the disclosure must convey the required information to one skilled in the art. "When the original specification accomplishes that [conveyance], regardless of how it accomplishes it, the essential goal of the description requirement is realized." Id. Thus, one must peruse the full scope of the disclosure, the working examples, the stated objectives, and all of the embodiments in order to determine whether in some way the written description conveys the invention to one skilled in the art. When this is done for the full disclosure in this case, applicants' specification meets the written description requirement of 35 U.S.C. § 112, first paragraph.

On page 23, the specification states:

> It is believed that this invention and many of its attendant advantages will be understood from its description above, and it will be apparent that various modifications can be made in the method and vaccine described above without departing from the spirit and scope of the invention or sacrificing all of its material advantages, the embodiments described above being merely preferred embodiments.

Applicants submit that the skilled artisan, having read the specification and the preferred embodiments describing the *Shigella* strains SC501, SC504, SC505, and SC506, would have

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been apprised that invention concerned additional strains, above and beyond, the preferred embodiments. These additional strains are what applicants have claimed in claims 13 and 14.

Applicants note that lack of literal support alone is not sufficient to support a rejection under 35 U.S.C. § 112, first paragraph. In re Wertheim, 541 F.2d 257, 265, 191 U.S.P.Q. 90, 98 (C.C.P.A. 1976). Applicants further note that the burden of showing that the claimed invention is not described in the specification rests on the Office in the first instance, and it is up to the Office to give reasons why a description not in *ipsis verbis* is insufficient. Id. Accordingly, applicants submit that the written description requirement of 35 U.S.C. § 112, first paragraph has been fulfilled, and respectfully request withdrawal of the rejection.

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance. If the Examiner should disagree, he is invited to contact the undersigned to discuss any remaining issues.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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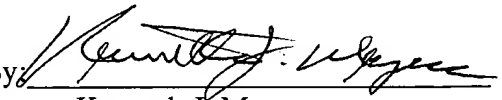
By: 
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Dated: January 20, 1999

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